PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
HUH Sang-Hoon
16th Fl. Woori Investment Bank Bldg.,
826-20 Yeoksam-dong, Kangnam-ku
135-080 Seoul
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PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)
(PCT Rule 71.1)

Date of mailing (day/month/year)	24 November 2004 (24.11.2004)
Applicant's or agent's file reference: 189	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority Date (day/month/year)
PCT/ KR 2003/001244	25 June 2003 (25.06.2003)	26 June 2002 (26.06.2002)

Applicant
KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the eleceted Offices.

3. Where required by any of the elected Offices, the Interational Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the eleceted Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/AT	Authorized officer
Austrian Patent Office Dresdner Straße 87 A-1200 Vienna/Austria FAX No. +43 / 1 / 53424-200	HOFBAUER Telephone No. +43 / 1 / 53424 - 225

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
189		
International application No.	International filing date (*day/month/year*)	Priority Date (*day/month/year*)
PCT/KR 2003/001244	25 June 2003 (25.06.2003)	26 June 2002 (26.06.2002)

International Patent Classification (IPC) or national classification and IPC

IPC^{7}: C07C 69/712, 67/31, C07D 263/58, 213/643, 241/18

Applicant

KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY

1. This international preliminary examination report has been prepared by this International Preliminary Examination Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I. ☒ Basis of the opinion
   - II. ☐ Priority
   - III. ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV. ☐ Lack of unity of invention
   - V. ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI. ☐ Certain documents cited
   - VII. ☐ Certain defects in the international application
   - VIII. ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.01.2004	5 November 2004 (05.11.2004)
Name and mailing address of the IPEA/AT Austrian Patent Office Dresdner Straße 87 A-1200 Vienna Facsimile No. 1/53424/200	Authorized officer MÜLLER-HIEL R. Telephone No. 1/53424/434

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PR[redacted]MINARY EXAMINATION REPORT

In[redacted]ional application No.
PCT/KR 2003/001244

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 2, 3, 5-19, 21 , as originally filed
pages _____ , filed with the demand
pages 1, 4, 20 , filed with the letter of 23 September 2004 (23.09.2004).

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages 22, 23 , filed with the letter of 23 September 2004 (23.09.2004).

☐ the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____.

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____.

☐ the claims, Nos. _____.

☐ the drawings, sheets/fig _____.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as „originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/KR 2003/001244

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-5	YES
	Claims	----	NO
Inventive step (IS)	Claims	1-5	YES
	Claims	----	NO
Industrial applicability (IA)	Claims	1-5	YES
	Claims	----	NO

Citations and explanations (Rule 70.7)

The following documents have been cited in the Search Report:

D1: GB 2038810 A
D2: JP 06247897 A2
D3: US 4531969 A
D4: US 4978774 A
D5: US 4550192 A
D6: DE 3409201 A
D7: EP 0157225 A
D8: EP 0062905 A

Document D1 (page 1, line 52 ff; claims 6-9) describes the esterification of a phenoxyphenol derivative (II) with the S-Isomer of a lactate derivative (III), wherein the leaving group X is preferably a methanesulfonyl group or a p-toluenesulfonyl group (page 2, line 22; claim 8). The reaction is carried out in the presence of a base, for example alkali metal carbonate (page 2, line 25), at a temperature range from 50 to 200°C (page 2, line 31; claim 9), in a suitable solvent, preferably a hydrocarbon, such as toluene or xylene (page 2, line 38), and yields the R-isomer of a phenoxyphenoxy propionic acid derivative (I). Continuous removal of water formed during the reaction is not mentioned in D1.
Accordingly, amended claims 1-5 of the application are acknowledged as novel over document D1.

Continuous removal of water formed during a reaction by azeotropic distillation is a routine method for a person skilled in the art. Nevertheless, this modification results in higher optical purities and yields, as mentioned in the description and explained in the letter from 23-9-2004. In the light of the teachings of D1, this result could not be anticipated. Therefore, an inventive step is acknowledged for amended claims 1-5.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V (page 1)

As indicated in the search report, documents D2-D8 merely describe the state of the art and are not considered of particular relevance concerning novelty and inventive step of the subject matter of the present application.

Industrial applicability is given.

VIII. Certain observations on the international application

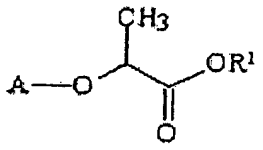
The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

New Claim 5 is a method claim characterized by the application of a certain apparatus. Such claims should be avoided. Instead, method claims should be characterized by process steps (eg. continous removal of water by azeotropic distillation). It is also noted, that an apparatus as mentioned in claim 5 and in the description is usually called "Dean-Stark trap".

PROCESS FOR PREPARING (R)-ARYLOXYPROPIONIC ACID ESTER DERIVATIVES

Technical Field

The present invention relates to a method for preparing optically active (R)-aryloxypropionic acid ester derivatives, and more particularly to a method for preparing (R)-aryloxypropionic acid ester derivatives represented by the following formula 1 with high optical purity and good yields at low cost via nulceophilic substitution reaction using phenol derivatives with various substituted functional groups and (S)-alkyl O-arylsulfonyl lactates as reactants in the presence of a proper solvent and a base at optimum temperature :



(1)

wherein R^1 is a C_{1-6} -alkyl or benzyl group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a phenoxyphenol group, a pyridyloxyphenyl group and a phenyloxynaphthyl group, wherein the aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a C_{1-4} -alkyl group, a C_{1-4} -haloalkyl group, a C_{1-4} -alkoxy group, and a C_{1-4} -haloalkoxy group.

Background Art

The compound represented by Formula 1, commonly called (R)-propionic

wherein R^1 is a C_{1-6} -alkyl or benzyl group; R^2 is a C_{1-6} -alkyl, phenyl group, or a phenyl group substituted with a C_{1-6} -alkyl or a C_{1-6} -alkoxy group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, a quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a phenoxyphenol group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein said aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a C_{1-4} -alkyl group, a C_{1-4} -haloalkyl group, a C_{1-4} -alkoxy group, and a C_{1-4} -haloalkoxy group.

Hereinafter, the present invention is described in more detail.

The present invention relates to a method for preparation of optically active (R)-propionic acid ester derivatives with high yield and good optical purity via nucleophilic substitution reaction using phenol derivatives and (S)-alkyl O-arylsulfonyl lactates as reactants, wherein the reactions are performed under a condition of solvent, temperature and leaving group, which are all specifically designed.

Phenol derivatives and (S)-alkyl O-arylsulfonyl lactates, reactants of the present invention as represented by the above Formulas 2 and 3, are known compounds and are synthesized by the known methods. For example, (6-chloro-2-benzoxazolyloxy)phenol can be prepared by a 4-step reaction using commercially available substances, such as aminophenol, urea, sulfuryl chloride, phosphorus pentachloride, and triethylamine, and solvents, such as xylene, acetic acid, chlorobenzene, and dichloroethane. And, (S)-alkyl O-arylsulfonyl lactate can be prepared by reacting (S)-alkyl lactate and arylsulfonyl chloride in the presence of triethylamine in dichloroethane solvent.

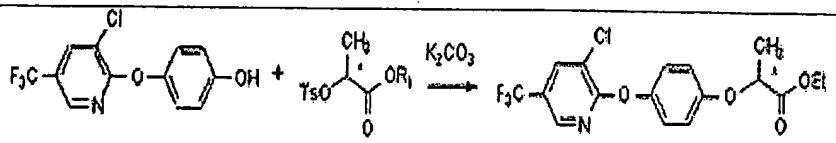
In the nucleophilic substitution reaction of the present invention, selection of

ketone	[redacted]			[redacted]	
*Ratio of (R)/(S) isomers: Identified by LC					

Comparative Example 2

The following Table 8 shows yields and ratio of optical isomers generated in the course of preparing (D+)-*n*-ethyl-2-[4-(3-chloro-5-trifluoromthylpyridine-2-yloxy)phenoxy]propionate (compound 29) according to the known methods shown in the reaction scheme 2.

Table 8



Reaction Solvent	Reaction Temperature	Reaction Time	Yield (%)	Ratio of (R)/(S) Isomers (%)*
Acetonitrile	Reflux	5 hours	72%	95.0/5.0
Methyl ethyl ketone	Reflux	5 hours	79%	80/20.0
Dimethylformamide	80 ~ 90℃	4 hours	70%	93.0/7.0
*Ratio of (R)/(S) isomers: Identified by LC				

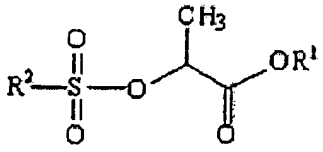
Comparative Example 3

The following Table 9 shows yields and ratio of optical isomers generated in the course of preparing (D+)-*n*-ethyl-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate (compound 32) according to the known methods shown in the reaction scheme 2.

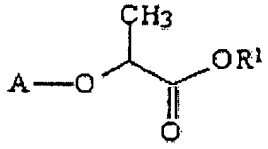
WHAT IS CLAIMED IS:

1. A method for preparing optically active (R)-aryloxypropionic acid ester derivatives represented by the following Formula 1 by reacting phenol derivatives represented by the following Formula 2 and (S)-alkyl O-arylsulfonyl lactate represented by the following Formula 3 in the presence of alkali metal carbonate in an aliphatic or aromatic hydrocarbon solvent under the temperature range of 60 to 100℃:

(2)



(3)



(1)

wherein water formed during the reaction is continuously removed, and

wherein R^1 is a C_{1-6} -alkyl or benzyl group; R^2 is a C_{1-6} -alkyl, phenyl group, or a phenyl group substituted with a C_{1-6} -alkyl or a C_{1-6} -alkoxy group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, a quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a phenyloxyphenyl group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein said aryl group can be substituted with 1-3 functional groups selected from the group consisting of a halogen atom, a nitro group, a nitrile group, an acetoxy group, a C_{1-4} -alkyl group, a C_{1-4} -haloalkyl group, a C_{1-4} -alkoxy group, and a C_{1-4} -haloalkoxy group.

2. In Claim [redacted]id hydrocarbon solvent is selected [redacted] the group consisting of toluene, xylene, cyclopentane, cyclohexane, methylcyclohexane, cycloheptane, *n*-hexane, and *n*-heptane.

3. In Claim 1, said solvent is cyclohexane or xylene.

4. In Claim 1, said method for preparing optically active (R)-aryloxypropionic acid ester derivatives is performed using potassium carbonate as a base in cyclohexane as a solvent at 80℃.

5. In Claim 1, the water is removed by using a flask equipped with a cooling condenser and Dean-Stock.

INVENTORS' OPINIONS

I. AMENDMENTS

We herein enclose redline-version and clean-version of Amendments for your convenient review.

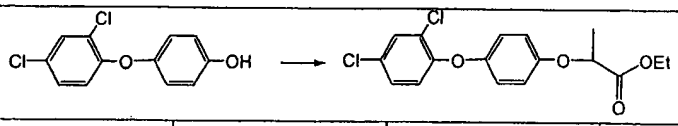
II. REMARKS

As shown in the presently amended claim 2 and the newly added claim 5, the present invention provides a method of preparing (R)-aryloxypropionic acid ester derivatives represented by the formula 1, wherein the optical purity and the yield are unexpectedly increased in view of the cited reference **by continuously removing water during the reaction, preferably by using a flask equipped with a cooling condenser and Dean-Stock.**

As it may be verified from the comparative experimental data, the present invention provides at least 10-20% higher optical purity compared with other conventional method as set forth in the originally-filed **TABLEs 6-9** (including that of D1 as shown in the following **TABLE 10.**

The following TABLE 10 provides optical purities and yields, which were (i) set forth in D1 (in a condition absent of solvent), and further obtained by the present inventors by using the method according to Example 1 in D1 (by using cyclohexane and xylene as a solvent). Considering the superiority in the optical purity and the yield in the present invention, the patentability of the present invention should also be acknowledged.

TABLE 10



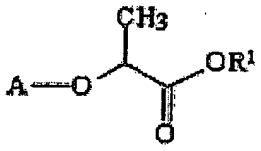
	Solvent	Reaction temp. (°C)	Reaction time (hrs)	ee (%)*	Yields (%)
D1	None (1)	150	8.5	90.2	72.0
	Cyclohexane (2)	81	16	90.4	87.0
	Xylene (2)	85	16	90.3	82.0
	Xylene (2)	100	16	82.0	90.0
The present invention	Cyclohexane	81	16	94.5	87.0
	Xylene	85	16	94.0	82.0
	Xylene	100	16	90.0	82.0

*Determined by using LC with chiral column
(1) Set forth in D1, p. 4, L. 20 (α_D = 24.7° at 23 °C)
(2) Obtained by accomplishing further experimentation according to Example 1 in D1

PROCESS FOR PREPARING (R)-ARYLOXYPROPIONIC ACID ESTER DERIVATIVES

Technical Field

The present invention relates to a method for preparing optically active (R)-aryloxypropionic acid ester derivatives, and more particularly to a method for preparing (R)-aryloxypropionic acid ester derivatives represented by the following formula 1 with high optical purity and good yields at low cost via nulceophilic substitution reaction using phenol derivatives with various substituted functional groups and (S)-alkyl O-arylsulfonyl lactates as reactants in the presence of a proper solvent and a base at optimum temperature :



(1)

wherein R^1 is a C_{1-6} -alkyl or benzyl group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a ~~*phenyloxyphenyl*~~ *phenoxyphenyl* group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein the aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a C_{1-4} -alkyl group, a C_{1-4} -haloalkyl group, a C_{1-4} -alkoxy group, and a C_{1-4} -haloalkoxy group.

Background Art

The compound represented by Formula 1, commonly called (R)-propionic

wherein R^1 is a C_{1-6} -alkyl or benzyl group; R^2 is a C_{1-6} -alkyl, phenyl group, or a phenyl group substituted with a C_{1-6} -alkyl or a C_{1-6} -alkoxy group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, a quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a ~~*phenyloxyphenyl*~~ *phenyloxyphenyl* group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein said aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a C_{1-4} -alkyl group, a C_{1-4} -haloalkyl group, a C_{1-4} -alkoxy group, and a C_{1-4} -haloalkoxy group.

Hereinafter, the present invention is described in more detail.

The present invention relates to a method for preparation of optically active (R)-propionic acid ester derivatives with high yield and good optical purity via nucleophilic substitution reaction using phenol derivatives and (S)-alkyl O-arylsulfonyl lactates as reactants, wherein the reactions are performed under a condition of solvent, temperature and leaving group, which are all specifically designed.

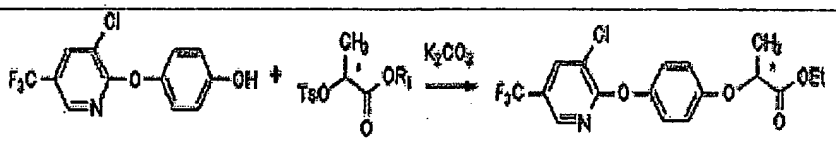
Phenol derivatives and (S)-alkyl O-arylsulfonyl lactates, reactants of the present invention as represented by the above Formulas 2 and 3, are known compounds and are synthesized by the known methods. For example, (6-chloro-2-benzoxazolyloxy)phenol can be prepared by a 4-step reaction using commercially available substances, such as aminophenol, urea, sulfuryl chloride, phosphorus pentachloride, and triethylamine, and solvents, such as xylene, acetic acid, chlorobenzene, and dichloroethane. And, (S)-alkyl O-arylsulfonyl lactate can be prepared by reacting (S)-alkyl lactate and arylsulfonyl chloride in the presence of triethylamine in dichloroethane solvent.

ketone					
*Ratio of (R)/(S) isomers: Identified by LC					

Comparative Example 2

The following Table 8 shows yields and ratio of optical isomers generated in the course of preparing (D+)-*n*-ethyl-2-[4-(3-chloro-5-trifluoromthylpyridine-2-yloxy)phenoxy]propionate (compound 29) according to the known methods shown in the reaction scheme 2.

Table 8



Reaction Solvent	Reaction Temperature	Reaction Time	Yield (%)	Ratio of (R)/(S) Isomers (%)*
Acetonitrile	Reflux	5 hours	72%	95.0/5.0
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Dimethylformamide	80 ~ 90℃	4 hours	70%	93.0/7.0
*Ratio of (R)/(S) isomers: Identified by LC				

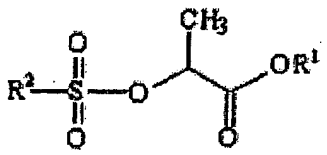
Comparative Example 3

The following Table 9 shows yields and ratio of optical isomers generated in the course of preparing (D+)-*n*-ethyl-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate (compound 32) according to the known methods shown in the reaction scheme 2.

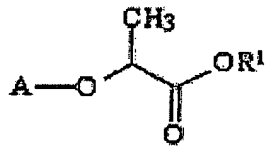
WHAT IS CLAIMED IS:

1. *(Amended)* A method for preparing optically active (R)-aryloxypropionic acid ester derivatives represented by the following Formula 1 by reacting phenol derivatives represented by the following Formula 2 and (S)-alkyl O-arylsulfonyl lactate represented by the following Formula 3 in the presence of alkali metal carbonate in an aliphatic or aromatic hydrocarbon solvent under the temperature range of 60 to 100℃:

(2)



(3)



(1)

wherein water formed during the reaction is continuously removed, and

wherein R^1 is a C_{1-6} -alkyl or benzyl group; R^2 is a C_{1-6} -alkyl, phenyl group, or a phenyl group substituted with a C_{1-6} -alkyl or a C_{1-6} -alkoxy group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, a quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a ~~*phenyloxyphenyl*~~ *phenoxyphenyl* group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein said aryl group can be substituted with 1-3 functional groups selected from the group consisting of ~~*a hydrogen atom,*~~ a halogen atom, a nitro group, a nitrile group, an acetoxy group, a C_{1-4} -alkyl group, a C_{1-4} -haloalkyl group, a C_{1-4} -alkoxy group, and a C_{1-4} -haloalkoxy

group.

2. In Claim 1, said hydrocarbon solvent is selected from the group consisting of toluene, xylene, cyclopentane, cyclohexane, methylcyclohexane, cycloheptane, *n*-hexane, and *n*-heptane.

3. In Claim 1, said solvent is cyclohexane or xylene.

4. In Claim 1, said method for preparing optically active (R)-aryloxypropionic acid ester derivatives is performed using potassium carbonate as a base in cyclohexane as a solvent at 80℃.

5. (New) In Claim 1, the water is removed by using a flask equipped with a cooling condenser and Dean-Stock.